Lung (2021) 199:83–84
https://doi.org/10.1007/s00408-021-00438-6

EDITORIAL

# Coming Soon: The First-Ever Drug(s) for Refractory Chronic Cough

**Peter V. Dicpinigaitis**[1]

Accepted: 5 March 2021 / Published online: 7 April 2021
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2021

Cough is the most common complaint for which patients in the United States seek medical attention [1]. Chronic cough is widely defined as a cough of greater than 8 weeks' duration, and is often due to a treatable underlying cause, such as upper airway cough syndrome (postnasal drip syndrome; rhinitis); asthma and non-asthmatic eosinophilic bronchitis; and gastroesophageal reflux disease (GERD) [2]. Chronic cough that does not respond to appropriate therapeutic trials aimed at underlying etiologies is termed refractory chronic cough (RCC). An additional term, unexplained chronic cough (UCC), has recently emerged to describe a chronic cough for which no underlying etiology is identified after adequate investigation [3]. The term Cough Hypersensitivity Syndrome proposes a mechanistic basis for chronic refractory or unexplained cough, that being vagal nerve hypersensitivity resulting in cough reflex hypersensitivity [4].

Appropriate treatment of an established underlying cause of chronic cough will usually be successful. Unfortunately, a significant percentage of patients will prove to have chronic cough refractory to all therapeutic interventions (RCC or UCC). For this subgroup of patients, few if any effective and well-tolerated therapeutic options exist. A minority of patients will obtain benefit from low-dose morphine [5], amitriptyline [6], gabapentin [7], or pregabalin and speech-language therapy [8]. Often, antitussive effect is achieved at the expense of intolerable side effects such as sedation. Thus, there exists a great unmet need for safe, effective, non-narcotic, non-sedating agents for the treatment of refractory chronic cough.

The last antitussive medication approved by the United States Food and Drug Administration (FDA) was benzonatate, in 1958 [9]. The widely used non-prescription antitussive, dextromethorphan, was approved in 1954 [9]. To date, there has not been a drug approved in the United States for the indication of chronic cough.

Thankfully, the last decade has witnessed significant scientific achievement in understanding the mechanisms of chronic cough, which has led to multiple clinical drug development programs exploring potential novel antitussive agents. The most advanced of these efforts is in the area of purinergic receptors, of which the P2X class functions as ligand-gated ion channels that are responsive to ATP [10]. In the airways, purines including ATP can trigger reflexes through the activation of vagal sensory nerves, and ATP may sensitize airway sensory nerves to tussive stimuli [10]. The P2X3 homotrimer and P2X2/3 heterotrimer have been implicated as most relevant in cough induction, with the latter also being essential to the sensation of taste [10]. The first-in-class P2X3 receptor antagonist, gefapixant, demonstrated significant antitussive effect in phase 2 trials, but at the expense of diminution of taste sensation in a significant subgroup of subjects [11]. Two phase 3 trials of gefapixant have been completed recently, and published data are awaited. Three additional drug development programs are ongoing, evaluating whether more selective P2X3 receptor antagonists may provide similar or better antitussive efficacy with less taste effect [10].

In this issue of *LUNG*, Morice and colleagues [12] provide a detailed description of a group of 253 subjects with RCC or UCC who had participated in a phase 2 clinical trial of gefapixant [11]. Enrollment criteria included duration of cough of at least one year; a subjective baseline cough severity score of ≥ 40 mm on a 100-mm visual analog scale (VAS) with 100 mm indicating most severe cough; and non-smoking status (either never smoker or cessation > 6 months prior to enrollment). Demographic characteristics of the subject population were quite consistent with those previously reported of patients seeking evaluation at specialty cough centers worldwide: predominance of women and lifetime non-smokers; mean age of patients 55 years, and most common age of presentation 60–69 years [13].

Although the very long median duration of cough (11 years) and high objectively measured median awake

✉ Peter V. Dicpinigaitis
pdicpin@gmail.com

[1] Albert Einstein College of Medicine and Montefiore Medical Center, 1825 Eastchester Road, Bronx, NY 10461, USA

cough frequency (28.9/h) observed in subjects in this study may be typical of patients evaluated at subspecialty cough centers, it will remain to be seen whether the efficacy demonstrated in clinical trials to date will be observed in a community-based population of patients with chronic cough for whom this therapy, once approved, will be prescribed. As in most clinical trials, there was a subgroup of non-responders to the therapeutic agent in this study. At present, one cannot predict a priori who will likely be a responder to therapy with a P2X3 antagonist. Although higher objectively measured baseline cough counts have been predictive in clinical trials, this observation will not inform community-based physicians prescribing the drug to patients. Furthermore, it will remain to be elucidated in post-approval surveillance how patients who experience both beneficial antitussive effect and taste disturbance will balance the two effects in terms of compliance with long-term therapy.

It is anticipated that the near future will bring the first-ever medications approved for chronic cough. This landmark achievement represents the culmination of years of effort by scientists and clinicians worldwide, and will provide desperately needed relief for patients afflicted by refractory chronic cough, and a therapeutic option for physicians treating this long-suffering group of patients.

## Declarations

**Conflict of interest** Peter V. Dicpinigaitis, MD, is the Editor-in-Chief of *LUNG*. He has served as a consultant to Merck, Bayer, Bellus Health, and Shionogi.

## References

1. Hsiao C-J, Cherry DK, Beatty PC et al (2010) National ambulatory medical care survey: 2007 summary. Natl Health Stat Report 27:1–32
2. Morice AH, Millqvist E, Bieksiene K et al (2020) ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J 55(1):1901136. https://doi.org/10.1183/13993003.01136-2019.Print2020Jan
3. Mazzone SB, McGarvey L (2020) Mechanisms and rationale for targeted therapies in refractory and unexplained chronic cough. ClinPharmacolTher. https://doi.org/10.1002/cpt.2003
4. Morice AH, Millqvist E, Belvisi MG (2014) Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. Eur Respir J 44:1132–1148
5. Morice AH, Menon MS, Mulrennan SA et al (2007) Opiate therapy in chronic cough. Am J Respir Crit Care Med 175:312–315
6. Ryan MA, Cohen SM (2016) Long-term follow-up of amitriptyline treatment for idiopathic cough. Laryngoscope 126:2758–2763
7. Ryan NM, Birring SS, Gibson PG (2012) Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. Lancet 380:1583–1589
8. Vertigan AE, Kapela SL, Ryan NM et al (2016) Pregabalin and speech pathology combination therapy for refractory chronic cough: a randomized controlled trial. Chest 149:639–648
9. Dicpinigaitis PV, Morice AH, Birring SS et al (2014) Antitussive drugs-past, present, and future. Pharmacol Rev 66:468–512
10. Dicpinigaitis PV, McGarvey LP, Canning BJ (2020) P2X3-receptor antagonists as potential antitussives: summary of current clinical trials in chronic cough. Lung 198:609–616
11. Smith JA, Kitt MM, Morice AH et al (2020) Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial. Lancet Respir Med 8(8):775–785. https://doi.org/10.1016/S2213-2600(19)30471-0
12. Morice AH, Birring SS, Smith JA et al (2021) Characterization of patients with refractory or unexplained chronic cough participating in a phase 2 clinical trial of the P2X3-receptor antagonist gefapixant. Lung, https://doi.org/10.1007/s00408-021-00437-7
13. Morice AH, Jakes AD, Faruqi S et al (2014) A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. Eur Respir J 44:1149–1155

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.